Component-resolved diagnostics can be useful for identifying hazelnut allergy in Japanese children

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A b s t r a c t

Background: Cor a 9 and Cor a 14 are effective markers for predicting hazelnut allergy. However, there have been no reports on the component-resolved diagnostics (CRD) of hazelnut allergy using an oral food challenge (OFC) for diagnosis in Asia. We hypothesized that CRD would improve the accuracy of diagnosing hazelnut allergies in Japanese children.

Methods: We recruited 91 subjects (median age: 7.3 years) who were sensitized to hazelnuts and had performed a hazelnut OFC at the National Hospital Organization Sagamihara National Hospital between 2006 and 2017. All subjects were classified as allergic or asymptomatic to 3 g of hazelnuts. The sIgE levels (hazelnut/Cor a 1/Cor a 8/Cor a 9/Cor a 14/alder pollen) were measured using ImmunoCAP. We aimed to determine the predictive factors of hazelnut allergy.

Results: Nine subjects (10%) were allergic to <3 g of hazelnuts. Levels of sIgE for Cor a 9 in hazelnut-allergic subjects were significantly higher than those in asymptomatic subjects (4.47 vs. 0.76 kUA/L, p = 0.039). Levels of sIgE to alder pollen and Cor a 1 in hazelnut-allergic subjects were significantly lower than those in asymptomatic subjects (<0.10 vs 13.0 kUA/L, p = 0.004; <0.10 vs 5.03 kUA/L, p = 0.025). The area under the receiver operating characteristics curve for hazelnut/alder/Cor a 1/Cor a 9 was 0.55/0.78/0.72/0.71, respectively, with p = 0.65/0.006/0.029/0.040, respectively.

Conclusions: The findings of a high sIgE level for Cor a 9 and a low sIgE level for Cor a 1 can improve the diagnostic accuracy to better identify Japanese children sensitized to hazelnuts.

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Introduction

Hazel nuts (Corylus avellana) belong to the same family of trees as birches and alders (family Betulaceae) and are commonly used in the food industry to prepare desserts such as pastries and chocolates. Hazelnuts are recognized as a common food allergen in Europe. In Japan, tree nuts are the eighth most common food that is associated with food allergies. If an allergy to a tree nut is suspected, the appropriate step would be to remove nuts from a patient’s diet even if they did not exhibit an allergic reaction or undergo an oral food challenge (OFC). Component-resolved diagnostics (CRD) can provide a more accurate diagnosis and assessment of the severity of the elicited symptoms, including for hazelnut allergy. Cor a 1, Cor a 8, Cor a 9, and Cor a 14 are the primary allergen components of sIgE antibodies and are used for diagnosing hazelnut allergy in Europe. In particular, sensitization to Cor a 9 (115 globulin storage protein) and Cor a 14 (2S albumin storage protein) has previously been reported as being associated with severe hazelnut allergy.

However, the sensitization pattern among hazelnut-allergic patients varies depending on their geographic backgrounds. To the best of our knowledge, there have been no studies that report on the utility of CRD for the diagnosis of hazelnut allergy based on an OFC in Asia. Therefore, the aim of our study was to investigate
whether CRD can improve the accuracy in diagnosing hazelnut allergy in Japanese children.

Methods

Subjects

We retrospectively analyzed data from children sensitized to hazelnuts and who had performed a hazelnut OFC at the National Hospital Organization Sagamihara National Hospital (Kanagawa, Japan) between August 2006 and July 2017. Patients with an equivocal response to hazelnut ingestion during or after the OFC were excluded from the study due to lack of accurate clinical data. We also excluded patients with missing laboratory data (Fig. 1).

Oral food challenge

The challenge food was prepared either at the National Hospital Organization Sagamihara National Hospital or by a guardian. We prepared the following three types of roasted hazelnut challenge foods: pumpkin cake with ground and roasted hazelnuts, hamburger with ground and roasted hazelnuts, and whole roasted hazelnuts served alone. If patients found it difficult to eat whole roasted hazelnuts, the addition of chocolate or cookies that do not contain hazelnuts was allowed. During the last 72 h before the OFC, we also excluded patients with missing laboratory data.

We further instructed all patients to perform an OFC with a higher hazelnut consumption to rule out OFC results.

We performed the OFC openly and set the total challenge dose at 0.5, 3.0, and 10 g of hazelnuts (68, 408, and 1360 mg of hazelnut protein, respectively). According to prior risk assessments of hazelnut allergies, the OFC was performed at one of the three doses. We further instructed all patients to perform an OFC with a higher total challenge dose. In particular, for patients who had a negative OFC result with <3 g of hazelnuts, we encouraged them to increase hazelnut consumption to ≥3 g.

The hazelnut OFC was conducted in 5, 3, 2, or single portions (Supplementary Table 1). With 5 portions, 1/16 of the total amount was administered first, and then 1/16, 1/8, 1/4, and 1/2 of the total amount was administered at successive 15 min intervals. For those with 3 portions, 1/8 of the total amount was administered first, and then 3/8 and 1/2 of the total amount was as administered at successive 30 min intervals. For those with 2 portions, 1/4 of the total amount was administered every 60 min. For those with a single dose, the total amount was administered at one time point. If symptoms were induced after administration of the first dose of an OFC test, the next administration was halted and appropriate treatment was started according to patient symptoms.

We assessed any symptoms induced by the OFC according to the grading of symptoms described in Supplementary Table 2. We judged an OFC as being positive when we observed objective symptoms greater than grade 2. We also regarded persistent subjective symptoms as likely positive symptoms. If grade 1 symptoms were not persistent, we continued the OFC and observed if other symptoms were induced. Anaphylaxis was defined according to the World Allergy Organization Anaphylaxis Guidelines. Patients were treated according to the European Academy of Allergy and Clinical Immunology’s (EAACI) food allergy and anaphylaxis guidelines.

Determination of hazelnut allergy

According to the OFC results and following any hazelnut ingestion that occurred at home after the OFC, the subjects were divided into two groups: 1) the allergic group, or children who reacted to ≤3 g of hazelnuts, and 2) the asymptomatic group, or children who did not react to ≥3 g of hazelnuts (Fig. 2).

Those with a positive OFC result with 0.5 g of hazelnuts were included in the allergic group (n = 2). Those with a negative OFC result with 0.5 g of hazelnuts were instructed to increase to ≥3 g of hazelnuts at home or encouraged to undergo an OFC with 3 or 10 g of hazelnuts. If any subject did not react to ≥3 g of hazelnuts, they were included in the asymptomatic group. If a subject reacted to ≤3 g of hazelnuts, they were included in the allergic group (n = 7).

Measurement of serum-specific IgE

The sIgE levels for hazelnut, Cor a 1, Cor a 8, Cor a 9, Cor a 14, and alder pollen were measured using the ImmunoCAP assay system (Thermo Fisher Scientific, Uppsala, Sweden). An sIgE level ≥0.35 kUA/L was considered positive for an allergy. Blood samples were collected across the range of 1 year before to 1 year after the OFC.

Outcome measures

After assessing the subjects’ backgrounds and their immunological test results, we compared the allergic and asymptomatic groups. We aimed to clarify predictors of hazelnut allergy by analyzing the participant characteristics, total IgE, hazelnut sIgE, and the sensitization pattern of the hazelnut allergen component of sIgE.

The background assessment of subjects included sex, age at the time of OFC, past history of immediate reaction to hazelnut, peanut, or any tree nut allergy, and any exhibiting any allergic complications at the time of the OFC. These data were collected from medical records and analyzed.

A total of 117 subjects who were sensitized to hazelnut received hazelnut OFC at the National Hospital Organization Sagamihara National Hospital from 2006 to 2017

Excluded, n=26
  • Missing laboratory data (n=21)
  • Missing clinical data (n=5)

91 subjects with definitive OFC results were included in the final analysis

Fig. 1. Study flow chart. A total of 91 patients participated in the study after inclusion and exclusion criteria were applied.
The results were expressed as medians, interquartile ranges, and 95% confidence intervals (CIs). The relationships between two variables were estimated using Spearman’s correlation coefficients; \( p < 0.05 \) were considered statistically significant. To compare differences between the two groups, we used Mann–Whitney U tests for continuous variables and Fisher’s exact tests for categorical variables; \( p < 0.05 \) were considered significant. Receiver operating characteristic curves (ROC) were generated for hazelnut sIgE, alder sIgE, Cor a 1 sIgE, Cor a 8 sIgE, Cor a 9 sIgE, and Cor a 14 sIgE. ROC curves were also generated for several ratios. Diagnostic performance of the variables was evaluated using the area under the curve (AUC). We calculated the hazelnut sIgE level for which approximately 5% or 10% of patients would have a clinical reaction to. This so-called 5% or 10% predictive decision point (PPV) is generally used as the value to decide whether an OFC should be performed. To identify the predictive factors for hazelnut allergy, logistic regression analysis was performed using a logarithm of the sIgE values.

Antigen-sIgE antibodies levels of \( <0.35\, \text{kU}\alpha/\text{L} \) were coded as \( 0.15\, \text{kU}\alpha/\text{L} \), \( 0.1\, \text{kU}\alpha/\text{L} \), \( 0.05\, \text{kU}\alpha/\text{L} \), and \( >100\, \text{kU}\alpha/\text{L} \). The sIgE values were analyzed by implementing the logarithm if necessary. Statistical analysis was performed with GraphPad Prism 7® (GraphPad Software, Inc., CA, USA) and R version 3.4.1 (2017, The R Foundation, Vienna, Austria).

**Ethical considerations**

In accordance with the Declaration of Helsinki, all procedures performed in this study and the risk of symptoms following OFC were fully explained to the patients and their guardians both verbally and in writing. Written informed consent, for both OFC and publication of the data, was obtained from all participants. The study design was approved by the Institutional Review Board of the National Hospital Organization Sagamihara National Hospital (approval no. 2016/16).

**Results**

**Enrollment of subjects and characteristics**

One hundred and seventeen patients who were sensitized to hazelnuts received OFCs with 0.5–10 g of roasted hazelnuts. We could not measure sIgE for the allergen component of hazelnut and alder pollen for 21 patients, and these patients were excluded due to missing laboratory data. Five patients were also excluded for missing clinical data. Therefore, our final analysis included 91 patients (Fig. 1).

Subject characteristics were summarized in **Table 1**. The median age was 7.3 years, and 69% were male. While 2 patients (2%) had a past history of immediate reaction to hazelnuts, neither of them had anaphylactic reactions. Thirty patients (33%) had a past history of immediate reaction to peanuts, and 31 patients (34%) had a history of immediate reaction to any tree nut except hazelnut. Current comorbidities of atopic dermatitis, bronchial asthma, allergic rhinitis, and allergic conjunctivitis were present in 60 (66%), 34 (37%), 41 (45%), and 11 (12%) of all participants, respectively. The total IgE level was 1180 IU/mL, and the levels of antigen-sIgE antibodies for hazelnut, alder, Cor a 1, Cor a 8, Cor a 9, and Cor a 14 were 8.47 kU\alpha/L, 8.15 kU\alpha/L, 3.85 kU\alpha/L, <0.10 kU\alpha/L, 0.84 kU\alpha/L, and 0.10 kU\alpha/L, respectively (expressed as medians).

We also compared the characteristics of excluded subjects (\( n = 26 \)) with those of the included subjects (\( n = 91 \)) in **Supplementary Table 3**.

**Diagnosis of hazelnut allergy**

The final decision regarding determining a diagnosis of an allergy to hazelnuts is shown in **Figure 2**. Nine patients (10%) were classified as having a hazelnut allergy, while 82 patients (90%) were asymptomatic. The induced symptoms and their severities are summarized in **Table 2**. The most common symptoms were gastrointestinal symptoms, which were observed in all 9 allergic patients (100%). All of these patients had a localized reaction such as oral discomfort, but 2 exhibited more extensive gastrointestinal symptoms including abdominal pain, diarrhea, and emesis. No patients developed neurological or cardiovascular symptoms.

Four patients (44%) had mild symptoms, which were mainly oral discomfort. Four (44%) had moderate symptoms. Only 1 patient (11%) had severe symptoms, which were generalized urticaria, repetitive cough, and throat tightness.

Anaphylaxis appeared in 3 patients (33%), with concomitant skin and respiratory symptoms in all cases; there were no patients with anaphylactic shock.

For treatment, oral antihistamine and \( \beta_2 \)-inhalation were used for 5 patients (56%) and 3 patients (33%), respectively. Only 1 patient (11%) used inhaled corticosteroids, which was based upon a decision by the patient’s mother in order to relieve respiratory symptoms following an OFC at home. None of the patients used adrenaline.

A comparison of patient characteristics between patients with a hazelnut allergy and those who were asymptomatic is presented in **Table 3**. There were no significant differences among the patients in the hazelnut-allergic group vs. the asymptomatic group in terms of sex, age, past history of immediate reaction to any food,
complications, and total IgE level. The observed doses of hazelnuts associated with a reaction were as follows: 3 patients reacted to 0.1–0.5 g of hazelnuts, 2 patients to 0.5–1 g, and 4 patients to 1–3 g. A comparison of sIgE in those with a hazelnut allergy vs. those in the asymptomatic group is shown in Figure 3. Hazelnut-allergic patients had significantly higher sIgE levels vs. those who were asymptomatic for Cor a 9 sIgE (4.47 vs. 0.76 kUA/L, p = 0.039), while patients with an allergy had significantly lower sIgE levels than asymptomatic patients for alder sIgE (<0.10 vs. 13.0 kUA/L, p = 0.004) and Cor a 1 sIgE (<0.10 vs. 5.03 kUA/L, p = 0.025). No significant differences were observed for hazelnut sIgE (11.0 vs. 8.43 kUA/L, p = 0.660), Cor a 8 sIgE (<0.10 vs. <0.10 kUA/L, p = 0.358), or Cor a 14 sIgE (0.60 vs. 0.10 kUA/L, p = 0.1318).

Receiver operating characteristic analysis

The AUCs for hazelnut sIgE, alder sIgE, Cor a 1, Cor a 8, Cor a 9, and Cor a 14 are shown in Table 4, to discriminate between the hazelnut-allergic and asymptomatic groups. The AUC for alder sIgE was highest (0.78; 95% CI: 0.61–0.95, p = 0.006), followed by Cor a 1 (0.72; 95% CI: 0.55–0.90, p = 0.029) and Cor a 9 (0.71; 95% CI: 0.52–0.89, p = 0.040).

The AUCs for hazelnut sIgE, Cor a 8, and Cor a 14 were 0.55 (95% CI: 0.36–0.73, p = 0.651), 0.58 (95% CI: 0.39–0.78, p = 0.406), and 0.65 (95% CI: 0.44–0.86, p = 0.151), respectively.

The AUCs for several sIgE ratios are presented in Supplementary Table 4. The AUC for the sIgE ratio of hazelnut/alder was highest (0.83; 95% CI: 0.72–0.95, p = 0.001), followed by Cor a 9/alder (0.80; 95% CI: 0.61–0.99, p = 0.004). The AUCs for these sIgE ratios were higher than that of alder sIgE alone.

Correlation between sIgE levels of allergen components

We analyzed the correlation coefficients between sIgE levels for hazelnut, alder, Cor a 1, Cor a 8, Cor a 9, and Cor a 14 (Supplementary Table 5). The sIgE levels for alder and Cor a 1 had a strong positive correlation (RS = 0.88, p < 0.001), followed by hazelnut and Cor a 1 (RS = 0.74, p < 0.001) and hazelnut and alder (RS = 0.73, p < 0.001) also had positive correlations.

### Table 1

Characteristics of subjects. Values are reported as n (%), median (interquartile range) as appropriate (n = 91).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazelnut asymptomatic group (n = 82)</th>
<th>Hazelnut allergic group (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>91</td>
<td>9</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>63 (69%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>7.3 (5.9–10.5)</td>
<td>7.6 (5.9–9.1)</td>
</tr>
<tr>
<td><strong>Past history of immediate reactions to</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazelnut</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Peanut</td>
<td>30 (33%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Tree nut except hazelnut</td>
<td>1 (1%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Any food</td>
<td>80 (88%)</td>
<td>7 (78%)</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>60 (66%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>34 (37%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>41 (45%)</td>
<td>4 (45%)</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>11 (12%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td><strong>Total IgE (IU/mL) (n = 88)</strong></td>
<td>1180 (507–2105)</td>
<td>245 (110–450)</td>
</tr>
<tr>
<td>sIgE (kUA/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazelnut</td>
<td>8.47 (3.30–23.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Alder pollen</td>
<td>8.15 (0.70–33.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Cor a 1</td>
<td>3.85 (&lt;0.10–25.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Cor a 8</td>
<td>&lt;0.10 (&lt;0.10–0.16)</td>
<td>NA</td>
</tr>
<tr>
<td>Cor a 9</td>
<td>0.84 (0.37–3.51)</td>
<td>NA</td>
</tr>
<tr>
<td>Cor a 14</td>
<td>0.10 (&lt;0.10–0.38)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Cor a 8, specific IgE.*

### Table 2

Symptoms and severity of the hazelnut allergic group. Data are expressed as n (%).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Hazelnut allergic group (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Nervous</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>3 (33%)</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

Predictive factors for hazelnut allergy

We performed univariate logistic regression analysis using the logarithm of the sIgE levels for hazelnut, alder, Cor a 1, and Cor a 9 to identify the predictive factors for hazelnut allergy. The calculated crude odds ratios of sIgE levels for hazelnut, alder, Cor a 1, and Cor a 9 were 0.72 (95% CI: 0.22–2.36, p = 0.583), 0.38 (95% CI: 0.19–0.75, p = 0.002), 0.45 (95% CI: 0.22–0.93, p = 0.013), and 2.38 (95% CI: 0.91–6.24, p = 0.070), respectively (Table 5).

sIgE levels for predicting hazelnut allergy

The sIgE levels that predict hazelnut allergy were calculated from the results of the logistic regression analysis. Regarding the hazelnut allergy outcome, the 5% and 10% PPVs for sIgE levels for alder, Cor a 1, and Cor a 9 were 7.68 and 1.32 kUA/L, 4.67 and 0.53 kUA/L, and 0.23 and 1.69 kUA/L, respectively. Furthermore, the 10% PPV for sIgE for hazelnut was 7.03 kUA/L, while the 5% PPV was not applicable (it was >101 kUA/L, which was beyond our observation) (Supplementary Table 6).

### Table 3

Characteristics of patients in the hazelnut asymptomatic or allergic group. Values are reported as n (%), median (interquartile range) as appropriate.

Discussion

We found that a high sIgE level for Cor a 9 and a low sIgE level for alder and Cor a 1 may indicate actual hazelnut allergies from a hazelnut-sensitized population.
The AUCs for sIgE to alder, Cor a 1, and Cor a 9 were high; therefore, determining sIgE for each of these parameters would improve diagnostic performance for hazelnut allergy, while using the overall sIgE level for hazelnut may not in fact be a reliable marker. We also calculated the crude odds ratio to describe probability curves for alder, Cor a 1, and Cor 9. Although we expected probability curves to be useful for assessing symptoms of hazelnut allergy, these curves did not seem to be practical for predicting hazelnut allergy due to the low odds ratios value.

Although Cor a 9 has been identified as a predictive marker for severe symptoms of hazelnut allergy in Europe, our novel finding was that Cor a 1 may also inversely be a reliable marker in Japanese children sensitized to hazelnuts.6,11,12 We hypothesized that the discrepancy between different markers used for diagnosing hazelnut allergy may come from variation in hazelnut sensitization patterns within a study population.

Cor a 1 can cross-react with the birch pollen allergen Bet v 1.11,18 In parts of Japan, including Kanagawa, alder pollen is more commonly found than birch pollen, except in Hokkaido and Nagano, where birch is mainly found. Figure 3 shows that our population consisted of alder pollen-sensitized patients. As confirmed by the strong correlation between sIgE and alder and Cor a 1 and hazelnut (Supplementary Table 5), we found that our study population had an elevated hazelnut sIgE level for alder-related cross-reactivity. This was not due to the primary sensitization to hazelnut itself.

The rate of hazelnut allergy in our study was lower than in previous studies. Previous studies have reported that 20%–40% of children who performed an OFC exhibited symptoms, though the characteristics of these populations differed from ours.5,19–21 Additionally, the severity of the induced symptoms in our study was milder than in prior studies, and anaphylaxis was less frequent. Regarding anaphylaxis elicited by hazelnut OFC, Brandström J et al.19 reported that hazelnut double-blind placebo-controlled food challenge tests (DBPCFC) induced anaphylactic symptoms affecting multiple organs in 50% of the participants and anaphylactic shock in 12.5% of the participants. In addition, 25% of the patients required treatment upon admission.

The discrepancy in results may be explained as follows: we used roasted hazelnuts so the allergenicity of hazelnuts could be reduced. Some studies reported that Cor a 1 is a heat- and digestion-labile PR-10 protein, whose allergenicity is reduced when subjected to the roasting process.1,22,23 In Japan, it is not customary to eat raw hazelnuts. Thus, while some previous studies have used raw hazelnuts,5,19–21 we used roasted hazelnuts in our study. Therefore, the rate of confirmed hazelnut allergy and the severity of the induced symptoms in our study may be different from those reported in previous studies. Additionally, not only the influence of cross-reactivity with pollen but also the accumulative dose of hazelnuts may help explain the difference in findings between ours

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**Table 4**

ROC curve predicts hazelnut allergy. In the table, areas under curve (AUC), including the 95% CI, are shown for several sIgEs (n = 91).

<table>
<thead>
<tr>
<th>sIgE (kUA/L)</th>
<th>AUC</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazelnut</td>
<td>0.55</td>
<td>0.36–0.73</td>
<td>0.651</td>
</tr>
<tr>
<td>Alder</td>
<td>0.78</td>
<td>0.61–0.95</td>
<td>0.006*</td>
</tr>
<tr>
<td>Cor a 1</td>
<td>0.72</td>
<td>0.55–0.90</td>
<td>0.029*</td>
</tr>
<tr>
<td>Cor a 8</td>
<td>0.58</td>
<td>0.39–0.78</td>
<td>0.406</td>
</tr>
<tr>
<td>Cor a 9</td>
<td>0.71</td>
<td>0.52–0.89</td>
<td>0.040*</td>
</tr>
<tr>
<td>Cor a 14</td>
<td>0.65</td>
<td>0.44–0.86</td>
<td>0.151</td>
</tr>
</tbody>
</table>

sIgE, specific IgE.

*Significant p value.

† Values are lower in the hazelnut allergic group.

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**Table 5**

Factors predicting a hazelnut allergy.

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log (Hazelnut sIgE)</td>
<td>0.72 (0.22–2.36)</td>
</tr>
<tr>
<td>Log (Alder sIgE)</td>
<td>0.38 (0.19–0.75)</td>
</tr>
<tr>
<td>Log (Cor a 1 sIgE)</td>
<td>0.45 (0.22–0.93)</td>
</tr>
<tr>
<td>Log (Cor a 9 sIgE)</td>
<td>2.38 (0.91–6.24)</td>
</tr>
</tbody>
</table>

OR, odds ratio; sIgE, specific IgE.
and those of previous reports. The previous studies set the accumulative hazelnut dose higher than our study did (in particular, ranging from 6 to 32 g of raw hazelnuts). As described later in this section, in our study, few patients consumed more hazelnuts after the OFCs. The discrepancy in results may be attributed to the small accumulative dose of hazelnuts.

Although Cor a 8, a lipid transfer protein (LTP), has been associated with severe hazelnut allergy in Mediterranean areas, it was not a reliable diagnostic marker of hazelnut allergy in our study. Such discrepancies in the effectiveness of Cor a 8 as a marker for diagnosing hazelnut allergy may be due to the differences in geography, ethnicity, and eating habits, which can influence the potential of sensitization to LTP. From a standpoint of LTPs, Pru p 3 in peach allergy resembles Cor a 8 in hazelnut allergy, which is not an effective marker to diagnose allergy in Japan but an effective marker to predict allergy in Mediterranean areas. For Mediterranean patients allergic to LTP, peach has been implicated as the primary sensitizer. Conversely, few Japanese patients with peach allergy are sensitized to LTP (Pru p 3). We speculate that as most Japanese children are sensitized to pollen, while few children are sensitized to LTP, both LTPs (Pru p 3 and Cor a 8) are not useful as diagnostic markers of peach and hazelnut allergies.

Hazel nut allergy varies from mild oral symptoms to severe systemic reactions. In fact, some patients in our study experienced anaphylaxis at a constant rate. We hypothesize these severe symptoms may be attributed to sensitization to Cor a 9.

However, in our study, most patients with a hazelnut allergy had mild or moderate symptoms. Additionally, the rate of a hazelnut allergy diagnosis was not as high as in previous European studies.

Therefore, in Japan, we recommend that hazelnut-sensitized patients who have a history of immediate reaction to peanuts or any tree nuts need not simply eliminate hazelnuts from their diet unless it is confirmed that the patient is actually suffering from a hazelnut allergy. As shown in Supplementary Table 6, we suggest that the hazelnut-sensitized patients with a higher sIgE level for Cor a 9 can safely consume hazelnuts.

However, consumption of hazelnuts may induce adverse reactions, including (in some cases) anaphylaxis. In light of this, patients, especially those outside the abovementioned parameters, should be encouraged to undergo an OFC using roasted hazelnuts (with ample consideration for patient safety).

There are some limitations in our study. First, we performed an open OFC, not a DBPCFCF. Since subjective symptoms, such as those associated with oral allergy syndrome (OAS), were observed in those with positive OFC results, DBPCFCFs would in theory be appropriate for diagnosing the allergy. However, most of the participants in our study had several concomitant conditions associated with food allergies. Hazelnut is not a common food in Japan, and an OFC is time-consuming for patients. These considerations and the incurred costs make it difficult to perform hazelnut DBPCFCFs.

Second, the number of hazelnut-allergic patients was limited within our study compared to the number of asymptomatic patients. Therefore, this may have reduced the statistical power of our results. In addition, we could not stratify the participants by age. We could not stratify the participants by age.

In conclusion, with the findings of a high sIgE level for Cor a 9 and a low sIgE level for Cor a 1, diagnostic testing can be improved for Japanese children sensitized to hazelnuts. Further prospective studies are needed to evaluate the validity of our results in another cohort with a larger sample size.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaillit.2019.10.001

Conflict of interest

The authors have no conflict of interest to declare.

Authors’ contributions

YI and SS designed the study and wrote the manuscript. YI, KT, and SS contributed to data collection. YI and KT performed the statistical analysis and interpretation of the results. SS, NY, HY, NS, and ME supervised the study and drafted the manuscript. All authors read and approved the final manuscript.

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